Remarks

Applicants respectfully request that the above amendments be entered after final as they place the claims in better form for allowance.

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 22-25, 28-33, 35, 37, and 40-42 are pending in the application, with 22, 28 and 37 being the independent claims. Claim 37 has been amended. Support for the amended recitation "in an aerosolized form" can be found at least on page 16, lines 21-23, Example 3 and Example 8. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Status of the Claims

Applicants wish to thank the Examiner for withdrawal of the previous rejections and for allowing claims 22-25, 28-33, 35 and 40-42.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claim 37 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,880,102 issued to George *et al.*, hereinafter "George", in view of U.S.

Patent No. 5,976,873 issued to Bohinski *et al.*, hereinafter "Bohinski" Applicants respectfully traverse the rejection.

In summary, the Examiner contends that George teaches recombinant adenoviral vectors encoding an NOS isoform operatively linked to a promoter, including the endothelial NOS isoform, for treatment of disease such as vein graft failure and restenosis in a mammal and administration of the NOS encoding adenoviral vector in saline (a pharmaceutically acceptable carrier which is further suitable for aerosol delivery). In addition, the Examiner contends that George teaches "the administration of adenoviral-NOS to lung tissue and further provides motivation for using tissue specific promoters...." (Paper No. 31, page 5).

The Examiner acknowledges that "George et al. does ***not*** specifically teach a pulmonary tissue specific expression control element." (Paper No. 31, page 5) (emphasis added). Applicants maintain that the mere reference to a tissue specific promoter, in George, does not suggest a "pulmonary tissue specific expression control element" as recited in claim 37.

Amended claim 37 no longer recites "suitable for aerosol delivery." Rather, it now recites that the composition "is in an aerosolized form." There is nothing in George that teaches or suggests aerosolized compositions. An aerosolized composition is not suggested by the teaching of the administration of an adenovirus vector with a NOS gene in saline. Regardless of whether the saline, adenovirus, NOS gene composition taught by George is suitable for aerosolization, the composition is only taught as a solution and not an aerosol. For example, "Treatment can be effected by infusing and expanding the vein segment to be grafted with a *solution* (eg saline solution) containing the NOS adenovirus (eg for approximately 15-30 minutes) prior to grafting." (Column 6, lines 13-16) (emphasis added).

The Examiner argues that Bohinski teaches "lung specific expression control elements that can be used in adenoviral vectors to direct expression of a therapeutic gene of interest in lung tissue." (Paper No. 31, page 5). In view of George's suggestion of tissue specific expression control elements and administering of Ad-NOS to lung tissue, the Examiner alleges that it would have been *prima facie* obvious to the skilled artisan to use the lung tissue specific expression control elements taught by Bohinski. Nowhere however, is there any motivation for combining George with Bohinski. Rather, the Examiner states that:

> based on the high level of skill in molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in modifying the adenoviral vector encoding NOS taught by George et al. to include a lung specific expression control element as taught by Bohinski et al. (Paper No. 31, page 5).

Bohinski does not cure the deficiencies of George. Both a motivation to combine the cited art, as well as a reasonable expectation of obtaining the claimed invention following combination of the art must be presented. Both motivation and expectation of success are necessary to establish a *prima fccie* case of obviousness. *In re Vaeck*, 20 U.S.P.Q. 1438, 1442 (Fed. Cir 1991). Merely because a high level of skill in the art may exist does not necessarily mean that there is a reasonable expectation of success of obtaining the invention upon combination of the art.

Solely in an effort to expedite prosecution and without acquiescing in the propriety of the rejection, Applicants have amended claim 37 to specify "wherein said composition is in an aerosolized form." Applicants assert that the combination of George in view of Bohinski does not teach a composition comprising a nucleic acid encoding a nitric oxide

synthase gene operably linked to a pulmonary tissue specific expression control element, an adenoviral vector and a pharmaceutically acceptable carrier vehicle, wherein said composition is in an aerosolized form. In light of the above arguments and amendment to claim 37, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claim 37 has been amended as follows:

37. (Thrice Amended) A pharmaceutical composition [suitable for aerosol delivery] comprising a nucleic acid encoding a nitric oxide synthase gene operably linked to a pulmonary tissue specific expression control element, an adenoviral vector and a pharmaceutically acceptable carrier vehicle, wherein said composition is in an aerosolized form.